Breast Cancer: A Focus on HER2 Targeted Therapy

Canadian Cardiac Oncology Network Meeting
Montreal
April 26th, 2019

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Disclosures

Dr Younis has participated in various advisory boards, and acted as consultant and expert witness, for Roche Canada (Trastuzumab, Pertuzumab, and TDM1)
Talk Objectives
Clinical Applications in Cardio-Oncology

✓ To highlight the role of anti-HER2 therapy in the management of HER2 positive breast cancers.
✓ To review the cardio-toxicity risks associated with anti-HER2 therapy in breast cancers.
✓ To illustrate the current management approach for anti-HER2 therapy associated cardiotoxicity.
Breast Cancer Subtypes

- HER2 positive
- ER / PR positive

Basal like

HER2 Enriched

Luminal
  Low Risk

Luminal
  High Risk
HER2 Testing
(IHC & FISH)

- Her-2/neu (red signals)
- CEB 17 (green signals)

“High-level Her-2/neu protein expression”
Systemic Therapy for Breast Cancer

0
Pre Invasive

I
Early Stage

II
Locally Advanced

III
Metastatic

Curative Intent
Local (Surgery +/- XRT) +/- Systemic
Survivorship (& Relapse)

Palliative Intent
Systemic +/- Local
End of Life Care

Adjuvant & (NeoAdjuvant)

Palliative
Trastuzumab Cardiotoxicity

- Taxol: 1%
- AC: 8%
- Taxol + TZ: 13%
- AC + TZ: 27%

Retrospective Review
Asymptomatic & Symptomatic Cardiac Dysfunction

Adjuvant Trastuzumab in Breast Cancer

Disease Free Survival

Yin et al, PLoS One 2011
## Adjuvant Trastuzumab Cardiotoxicity

<table>
<thead>
<tr>
<th>Cochrane Meta-Analysis</th>
<th>↓ LVEF</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab (n= 5471)</td>
<td>11.2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Control (n=4810)</td>
<td>5.6%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Relative Risk (95%CI)  
- Trastuzumab vs Control: 1.83 (1.36 -2.47) vs 5.11 (3.00-8.72)

Anti HER2 based Therapy for Breast Cancer

**Benefit**

Early Stages: ↓ Relapse & ↑ OS  
Metastatic: ↑ QOL & ↑ OS

**Risk**

Cardio-Toxicity
Trastuzumab Cardiotoxicity (Risk Factors)

**Patient**
- Older Age
- Lower Baseline LVEF% (or CHF)
- Underlying CVS Risks (HTN, CAD, AF, DM, Obesity, Dyslipidemia, Renal Failure)

**Treatment**
- Longer vs Shorter Anti HER2 therapy
- Concurrent vs Sequential Therapy
- Anthracycline Use (current or past)
Trastuzumab Cardiac Toxicity
(Duration of Trastuzumab Therapy)

Cumulative Incidence of Cardiac Endpoints*

* Competing risk analysis with disease-free survival events considered as competing risks. The majority of cardiac events are reversible (Proctor et al. JCO 2010)

HERA Trial

Goldhirsch et al, SABCS 2012
# Trastuzumab Cardiac Toxicity (Duration of Trastuzumab Therapy)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Longer (1-Year) vs shorter (6 or 3 Months)</th>
</tr>
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<tbody>
<tr>
<td>DFS</td>
<td>HR = 1.13; 95% CI 1.03–1.25; p=0.01</td>
</tr>
<tr>
<td>OS</td>
<td>HR = 1.16; 95% CI 1.01–1.32; p=0.03</td>
</tr>
<tr>
<td>Cardiac</td>
<td>OR = 0.52; 95% CI 0.43–0.62; p &lt; 0.00001</td>
</tr>
</tbody>
</table>

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**Meta-Analysis**

Six studies (11,496 Patients)  

Chen et al, Cancer Treat Rev 2019
### Trastuzumab Cardiac Toxicity
Concurrent vs Sequential

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Sequential</th>
<th>Concurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N 9831</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>0.0%</td>
<td>2.2%</td>
<td>3.3%</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.0-0.7%)</td>
<td>(1.1-3.8%)</td>
<td>(2.0-5.1%)</td>
</tr>
</tbody>
</table>

At 9 months analysis (500 patients per arm) for normal or \( \leq 15 \% \) decrease in LVEF after AC. Concurrent received 3 additional months of Trastuzumab.

Perez et al. Proc ASCO 2005
### BCIRG 006 Trial

<table>
<thead>
<tr>
<th>Arm</th>
<th>CHF</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AC → T</td>
<td>7</td>
<td>(0.7%)</td>
</tr>
<tr>
<td>AC → TH</td>
<td>21</td>
<td>(2.0%)</td>
</tr>
<tr>
<td>TCH</td>
<td>4</td>
<td>(0.4%)</td>
</tr>
</tbody>
</table>

No Cardiac Deaths. CHF NYHA G3-4

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#### Disease-Free Survival

- AC → TH: 84% at 6 years (HR = 0.75, p = 0.04)
- TCH: 75% at 6 years (HR = 0.64, p < 0.001)

#### Overall Survival

- AC → TH: 92% at 6 years (HR = 0.77, p = 0.04)
- TCH: 91% at 6 years (HR = 0.63, p < 0.001)

Slamon et al, NEJM 2011
Real-World Trastuzumab CardioToxicity
“OHERA Observational Study”

3733 Patients (Stages I-IIIB)

CHF NYHA II-IV : 2.8%
Cardiac Deaths : 0.2%*
CHF Resolution : 73%

*All with cardiac disease history

CHF Risk Factors

• Age ≥ 65
• Cardiac History
• Hypertension
• CVS Medications
• Baseline LVEF ≤ 55%

Lidbrink et al, Breast Cancer Research Treatment 2019
Anti HER2 Systemic Therapy for Breast Cancer

Baselga et al, Crit Rev Oncol Hematol. 2017
<table>
<thead>
<tr>
<th></th>
<th>Cap + Lap</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac dysfunction AEs</strong>&lt;sup&gt;a&lt;/sup&gt;, n (%)</td>
<td>(n=488)</td>
<td>(n=490)</td>
</tr>
<tr>
<td>All grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Lowest post-baseline LVEF value, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥45%</td>
<td>454 (98.5)</td>
<td>476 (98.8)</td>
</tr>
<tr>
<td>≥40 to &lt;45%</td>
<td>4 (0.9)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>&lt;40%</td>
<td>3 (0.7)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>LVEF &lt;50% and ≥15-point decrease from baseline, n (%)</td>
<td>(n=445)</td>
<td>(n=481)</td>
</tr>
<tr>
<td></td>
<td>7 (1.6)</td>
<td>8 (1.7)</td>
</tr>
</tbody>
</table>

Verma et al, NEJM 2012
Anti HER2 Systemic Therapy for Breast Cancer

Adjuvant
- Trastuzumab + Chemo
- Trastuzumab + Chemo +/- Pertuzumab
- Trastuzumab + Chemo +/- TDM1

NeoAdjuvant
- Trastuzumab + Chemo +/- Pertuzumab
- Trastuzumab + Chemo +/- TDM1

Combination Treatment NOT associated with ↑↑ Cardiotoxicity
- Trastuzumab + Chemo +/- Pertuzumab
- TDM1
- Capecitabine + Lapatinib
Prevention: Exercise & Prophylactic Medications

Cardio-Oncology Clinics

Cardio-Toxicity Management

Baseline history, physical exam, assessment of LVEF; consider baseline troponin and global longitudinal strain in high-risk patients.

High-risk: LVEF 50-55%, or age ≥60 years, or ≥2 risk factors for cardiotoxicity, does not meet criteria for extreme high-risk.

Low-risk: LVEF >50%.

Risk factors:
- Cardiac history
- Diabetes
- Hypertension
- Smoking history
- Family history
- Prior treatment with anthracyclines
- Prior treatment with taxanes
- Prior treatment with trastuzumab

Baseline LVEF ≥50%:
- Continue medical therapy for HER2 therapy unless the benefit exceeds the HF risk (see text).
- HER2 tumor: decrease in LVEF ≥10% or to ≤50%.
- HER2 tumor: LVEF <50% and/or symptomatic HF:
  - Initiation of HER2 therapy.
  - Initiation of ARB and beta-blocker; reassessment in 4 weeks.
- HER2 tumor: Asymptomatic and LVEF ≥50%:
  - Initiation of ARB and beta-blocker; reassessment in 4 weeks.
  - LVEF <50% and/or symptomatic HF:
    - Initiation of HER2 therapy.
- Asymptomatic and LVEF ≥60%:
  - Continue medical therapy for HER2 therapy.
Trastuzumab-based Therapy for Breast Cancer

**Benefit**
- Early Stages: ↓ Relapse & ↑ OS
- Metastatic: ↑ QOL & ↑ OS

**Risk**
- Cardio-Toxicity

**Prognostic & Predictive**

**Patient Selection & Management**
Conclusions

- Anti-HER2 therapy is a pivotal component of the current treatment of HER2 positive breast cancer.
- The predominant concerning adverse event during anti-HER2 based therapy is cardiotoxicity.
- Anti HER2 therapy decisions depend on predicted benefits and anticipated / encountered cardiotoxicities.
- The role of preventive measures for cardio-toxicity within treatment paradigms require further research.
In the era of improved breast cancer outcomes achieved with refined anti HER2 therapy, the management (& prevention) of associated cardio-toxicities is critical.